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Sociodemographic and lifestyle variables are compound- and class-specific correlates of urine phytoestrogen concentrations in the US population[1,,2,,3,,4]

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Abstract

Isoflavones and lignans are plant-derived dietary compounds generally believed to be beneficial to human health. We investigated the extent to which sociodemographic (age, sex, race-ethnicity, education, and income) and lifestyle variables (smoking, alcohol consumption, BMI, physical activity, and dietary supplement use) were correlates of spot urine concentration for daidzein (DAZ), genistein (GNS), O-desmethylangolensin (DMA), equol (EQU), enterodiol (ETD) and enterolactone (ETL) in the US population ≥20 y (NHANES 2003–2006). We performed correlation analyses with continuous variables and calculated stratified unadjusted geometric means for each sociodemographic and lifestyle variable. We used bivariate significance testing and covariate adjustment by use of multiple regression models to identify influential variables, and used *beta* coefficients to estimate relative effects. Urine creatinine was also included in our analyses because of its use in correcting for variable dilution in spot urine samples. We observed many statistically significant (P <0.05) associations with the sociodemographic and lifestyle variables that withstood covariate adjustment. Smoking was a significant correlate of urine DMA and ETL, with concentrations at least 25% lower in smokers vs. nonsmokers. Consumers of 1 daily alcoholic drink vs. none were estimated to have 18–21% lower urine EQU and DMA concentrations. A 25% increase in BMI was associated with 21% lower urine ETL, and increasing physical activity was associated with >6% higher urine ETL concentrations. Dietary supplement use was not significantly associated with any of the urine phytoestrogens. Overall, we found that relationships between sociodemographic and lifestyle variables and urine phytoestrogen concentration were highly compound- and class-specific.

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[3]Supplemental Tables 1–3 and Supplemental Figure 1 are available as Online Supporting Material with the online posting of this paper at http://jn.nutrition.org.

[4]Abbreviations used: ALT, alanine aminotransferase; AST, aspartate aminotransferase; DAZ, daidzein; DLS, Division of Laboratory Sciences; DMA, O-desmethylangolensin; EQU, equol; ETD, enterodiol; ETL, enterolactone; GNS, genistein; MA, Mexican American; MET, metabolic equivalent task; NCHS, National Center for Health Statistics; NCEH, National Center for Environmental Health; NHB, non-Hispanic black; NHW, non-Hispanic white; PIR, poverty income ratio.

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Introduction

Isoflavones and lignans are plant-derived dietary compounds generally believed to be beneficial to human health (1). Soybeans and soy-based products such as soy flour, soy milk, miso, tofu and tempeh are major dietary sources of isoflavones (2). Seeds such as linseed, flaxseed and sesame seeds are conspicuous sources of lignans; however, most dietary consumption of lignans originates from more ubiquitous, lower-concentration sources such as seed oils, whole grain cereals, beans, and other fruits and vegetables (1). Isoflavones and lignans are commonly referred to as phytoestrogens, a class of compounds capable of some degree of direct or metabolite-mediated estrogenic activity in the human body. The pseudoestrogenic behavior of these compounds has been postulated as an antagonistic mechanism that reduces the risk of hormone-dependent cancers such as breast (3,4) and prostate cancer (5,6), and may also have an effect on other hormone-dependent conditions such as menopausal symptoms (7). Phytoestrogens have also been studied in the context of health conditions and diseases unrelated to their phytoestrogenic activity, such as cardiovascular disease risk (8,9). Concerns with phytoestrogen consumption have also been raised, in particular the potential risk for developmental abnormalities in infants from isoflavone exposure (10).

The NHANES is a program of continuous studies designed and conducted by the CDC for the purpose of assessing the health and nutritional status of the US population (11). From 1999 to 2010, the NHANES datasets have included spot urine concentration measurements for 6 phytoestrogens in study participants 6 y and older: two plant isoflavones—daidzein (DAZ)[4] and genistein (GNS); two enterogenous DAZ metabolites—equol (EQU) and O-desmethylangolensin (DMA); and two enterolignans—enterolactone (ETL) and enterodiol (ETD) (Supplemental Figure 1). Urine and serum/plasma concentrations of these compounds can serve as indicators of dietary isoflavone and lignan intake (12,13), and so their measurement in cross-sectional studies such as the NHANES can go beyond simply assessing exposure and provide insight on population's dietary habits. Most recently, the NHANES urine phytoestrogen data for 2003–2006 was analyzed and presented in the CDC's *Second National Report on Biochemical Indicators of Diet and Nutrition in the US Population 2012* (*Second Nutrition Report*) (14,15), the latest in a series of publications providing descriptive statistics on nutritional and diet-related biologic indicators as a tool for establishing reference levels, identifying disparities, tracking trends over time and evaluating the effectiveness of public health interventions. The NHANES urine phytoestrogen data has been used in other similar descriptive analyses (16,17).

Select urine phytoestrogens in NHANES have been examined in relation to specific variables such as dietary isoflavone intake (18), dairy consumption (19) and serum lipids (20), but to the best of our knowledge, no comprehensive analyses of the association of commonly studied sociodemographic and lifestyle variables with urine phytoestrogens in the NHANES exists. Peeters *et al*. (21) looked at the variance in plasma phytoestrogen

[4]Abbreviations used: ALT, alanine aminotransferase; AST, aspartate aminotransferase; DAZ, daidzein; DLS, Division of Laboratory Sciences; DMA, O-desmethylangolensin; EQU, equol; ETD, enterodiol; ETL, enterolactone; GNS, genistein; MA, Mexican American; MET, metabolic equivalent task; NCHS, National Center for Health Statistics; NCEH, National Center for Environmental Health; NHB, non-Hispanic black; NHW, non-Hispanic white; PIR, poverty income ratio.

concentrations explained by geographic, sociodemographic, lifestyle and laboratory variables in 1414 subjects from the European Prospective Investigation into Cancer and Nutrition study. Kikkinen *et al*. (22) studied various determinants of serum ETL concentration in 2380 Finnish adults (25–46 y). Chun *et al*. (18), reported data for urine DAZ, DMA, EQU and GNS from NHANES 1999–2000 stratified by sociodemographic and lifestyle variables in an attempted validation of isoflavone intake study; however, their reported values are inconsistent with other analyses of the NHANES 1999–2000 data (14,16,17) and their reported sample size exceeds the number of urine phytoestrogen observations in the NHANES 1999–2000 data set (23). Sociodemographic and lifestyle variables have also been studied as determinants of biologic phytoestrogen concentrations in smaller settings such as DAZ-metabolizing phenotypes in US (24) and Japanese (25) women. Of all these studies, the work of Kikkinen *et al*. (22) is the most comparable example of a systematic study of sociodemographic and lifestyle variables in which modeling for covariate effects was considered, albeit for a single biomarker (serum ETL).

The goal of our study was to assess the combined association of specific sociodemographic (age, gender, race-ethnicity, education, and poverty income ratio [PIR]) and lifestyle variables (smoking, alcohol consumption, BMI, physical activity, and dietary supplement use) with urine phytoestrogen concentrations from NHANES 2003–2006 as a logical extension of the *Second Nutrition Report*. Similar analyses were also conducted for companion publications on water-soluble (26) and fat-soluble (27) nutrients, trace elements (28) and acrylamide (29). The common purpose of these analyses was to better understand the demographic differentials in biomarker concentrations observed in the *Second Nutrition Report*, as well as provide a foundation of knowledge to researchers who develop predictive models or address specific hypotheses.

Participants and Methods

Survey design and participants

The NHANES collects cross-sectional data on the health and nutritional status of the civilian noninstitutionalized US population (11). Since 1999, the National Center for Health Statistics (NCHS) at the CDC has conducted NHANES as a continuous survey with data released in 2-y cycles. The survey obtains a stratified, multistage, probability sample designed to represent the US population on the basis of age, sex, and race-ethnicity. All respondents gave their informed consent, and the NHANES protocol was reviewed and approved by the NCHS Research Ethics Review Board. Interview and examination response rates for each survey period are publically available (30).

Laboratory methods

Spot urine specimens from a 1/3 subset of participants from the 2003–2004 NHANES cycle were analyzed for urine phytoestrogens by use of HPLC-MS/MS with electrospray ionization (31,32). Aliquots from the 2005–2006 NHANES cycle were analyzed for the same analytes by use of HPLC-MS/MS with atmospheric pressure ionization (33,34). Good agreement has been demonstrated between results obtained by the 2 methods (33). All reported results satisfied the requirements of a multi-rule quality control system (35).

Study variables

The following sociodemographic and lifestyle variables and categories were used in our analyses: sex (male, female); age (20–39 y, 40–59 y, ≥60 y); race-ethnicity (Mexican American [MA], non-Hispanic black [NHB], non-Hispanic white [NHW]); education (<high school, high school, >high school); PIR (≤1.85 [low], >1.85–≤3.5 [medium], >3.5 [high] (36,37); smoking (serum cotinine ≤10 μg/L [non-smoker], >10 μg/L [smoker]) (38); alcohol consumption (average daily number of "standard" drinks: no drinks, >0–<1 drink/d, ≥1–<2 drink/d, ≥2 drink/d); BMI (kg/m^2: <18.5 [underweight], ≥18.5–<25.0 [normal], ≥25.0–<30.0 [overweight], ≥30.0 [obese]); physical activity (metabolic equivalent task [MET]-min/wk from leisure time physical activity: none, >0–<500, ≥500–<1000, ≥1000 MET-min/wk) (39); supplement use (reported taking a dietary supplement within the past 30 d: yes [user], no [non-user]). The following variables were also assessed: liver dysfunction (aspartate aminotransferase [AST] or alanine aminotransferase [ALT] >70 U/L [impaired], AST and ALT ≤70 U/L [normal]), because of its relationship with phytoestrogen metabolism; and urine creatinine (continuous) because of its use in correcting for variable dilution in spot urine samples. Gender, age, race-ethnicity, education, PIR, alcohol consumption and supplement use were self-reported by study participants. BMI was determined using height and weight measurements performed by trained examiners. Laboratory methods for serum AST and ALT, serum cotinine, and urine creatinine are described elsewhere (32,34).

Analytic sample

All Mobile Examination Center-examined NHANES 2003–2004 and 2005–2006 participants ≥20 y with at least 1 urine phytoestrogen measurement were eligible for inclusion in our study. Individuals who reported antibiotics within the past 30 d were excluded because of potential effects on enterogenous phytoestrogen metabolism via gut microbiota. No study participants were excluded based on health variables. Based on these criteria data were available for approximately 3000 participants (Supplemental Table 1).

Statistical analyses

A companion publication by Sternberg et al. (40) provides complete details of the statistical approaches used in this analysis. Sternberg et al. also discuss the approaches used in developing the multiple regression models due to the limited degrees of freedom, such as the number of covariates considered, the forms chosen for continuous covariates, and how interactions between covariates were addressed.

Urine phytoestrogen distributions were highly right-skewed; log-transformation corrected this, and was used along with the calculation of geometric means when parametric tests were performed. Spearman correlations were used to explore bivariate associations between each urine phytoestrogen and selected continuous variables. Bivariate associations for categorical variables were explored by presenting the geometric means and 95% CI for each urine phytoestrogen across the categories. Geometric means were compared across categories by use of Wald F tests. Simple linear regression was used to provide an accompanying measure of the percent of the total variability in the urine phytoestrogen that is explained by a single covariate (Model 1 r^2).

Multiple linear regression was used to assess the impact of confounding and determine whether statistical significance persists after adjusting for differences in key variables. In all cases the dependent variable was the natural log transformation of the urine phytoestrogen concentration. We used the independent variable as a continuous variable when possible. Alcohol consumption, BMI, and physical activity were log-transformed because these variables tend to be skewed right. The predictor variables were arranged into 3 "chunks": sociodemographic variables (age, sex, race-ethnicity, education level, PIR); lifestyle variables (smoking, alcohol consumption, BMI, physical activity level and dietary supplement use); and urine creatinine. Independent variables were tested in a hierarchical, chunk-wise fashion such that each chunk of related variables was tested simultaneously to determine which independent variables were related to the dependent variable. The influence of each chunk was assessed by a Satterthwaite adjusted F chunk test. For each model the coefficient of multiple determination (R^2) was calculated to provide a measure of the percent of the total variability in the urine phytoestrogen concentration that the model explains. Wald F *P*-values indicated whether any single *beta* coefficient was significantly different from 0.

The results of 4 regression models were summarized for each urine phytoestrogen: simple linear regression (Model 1); multiple linear regression with the sociodemographic chunk (Model 2); multiple linear regression with both sociodemographic and lifestyle chunks (Model 3); and multiple linear regression with the sociodemographic and lifestyle chunks, and urine creatinine (Model 4). All variables were retained in all models to allow for uniform presentation and comparison of results across all urine phytoestrogens. The results from each of the models were summarized by presenting the predicted percent change in urine phytoestrogen concentration with change in each covariate, holding all other remaining covariates constant.

Results

Descriptive information of the respondent characteristics in the NHANES 2003–2004 and NHANES 2005–2006 samples for urine phytoestrogens can be found in Supplemental Table 2. Spearman correlation analyses were performed between urine phytoestrogen concentrations and continuous lifestyle and sociodemographic variables, as well as urine creatinine concentrations (Table 1). With the exception of creatinine, significant correlations were weak (Spearman $|r|<0.2$). Consistencies were observed in some cases among phytoestrogen classes, namely plant isoflavones (DAZ and GNS), DAZ metabolites (EQU and DMA), and enterolignans (ETD and ETL). Weak to moderate, statistically significant correlations ($0.18 \leq |r| \leq 0.40$) were observed for creatinine with all phytoestrogens.

Bivariate methods (Model 1) were used to describe the association of individual sociodemographic variables, lifestyle variables, and urine creatinine concentrations with urine phytoestrogen biomarker concentrations (Table 2). Sociodemographic and lifestyle variables were significantly ($P < 0.05$) related to urine phytoestrogen concentrations in limited cases. Race-ethnicity had very highly significant ($P < 0.0001$) associations with DAZ metabolites (EQU, DMA), and similarly significant associations were also seen with alcohol consumption ($P = 0.0031$ for EQU, $P < 0.0001$ for DMA). Lifestyle variables resulting in

highly significant relationships included smoking status (ETL, $P = 0.0002$) and physical activity (ETL, $P = 0.0006$). Supplement use was the only variable that was not significantly associated with biomarker status. Although significant relationships were observed for several of the variables, the degree to which they explained the variability observed (based on model r^2 value) was miniscule (<2%).

Multiple regression models were used to determine the percentage of biomarker variation explained by each chunk of study variables (Supplemental Table 3). From 1% to 2% of the observed variability in phytoestrogen biomarker concentration was attributable to the sociodemographic variables (Model 2). Except for the plant isoflavones (DAZ, GNS), the addition of lifestyle variables (Model 3) further increased the amount of variability in biomarker concentration explained, with the largest increases observed for the mammalian (i.e. enterogenous) phytoestrogens ETL (4%), DMA and EQU (3%). Further addition of urine creatinine (Model 4) had the greatest impact; the model combining creatinine with sociodemographic and lifestyle variables accounted for 8–17% of the variability in biomarker concentrations.

Beta coefficients from multiple regression models were used to estimate the percent change in biomarker concentrations expected with changes in a given variable both before and after adjusting for sociodemographic variables, lifestyle variables, and urine creatinine concentration (Table 3; *beta* coefficients provided in Supplemental Table 3). Before any adjustments (Model 1) the largest difference was observed with smoking, where DMA and ETL concentrations were estimated to be at least 30% lower in smokers vs. nonsmokers. Sex had a notable relationship with plant isoflavone concentrations, with urine DAZ and GNS estimated to be at least 15% lower in females vs. males. Urine DAZ was estimated to be 14% lower in MA vs. NHW, and even larger differences were observed for DAZ metabolites (−36% for EQU, −58% for DMA). Urine EQU concentrations were estimated to be 24% lower in NHB vs. NHW. The consumption of 1 alcoholic drink/d was associated with lower urine concentrations of daidzein metabolites (-18% for EQU and −29% for DMA). PIR was a significant correlate of enterolignan and DMA concentration; ETD and ETL were 17% and 14% lower, respectively, and DMA was 21% lower with a 2 unit decrease in PIR. Education was also a notable correlate of urine DMA and ETD, with concentrations 24–27% lower in individuals with only a high school education or less. Urine ETL concentrations changed with lifestyle variables related to overall physical fitness, being 13% lower with a 25% increase in BMI and 7% higher with increasing physical activity (MET 750 min/wk vs. 150 min/wk). With some exceptions, adjusting for sociodemographic or sociodemographic and lifestyle variables generally did not have a prominent effect on the estimated percent changes in urine biomarker concentrations. Adjusting for creatinine had substantial influence on the percent changes estimated in the biologic sociodemographic variables and often inverted the direction of the relative biomarker difference observed. The previously noted sex differences for DAZ and GNS were no longer significant, and new significant differences appeared for EQU (19%), DMA (29%), and ETD (37%), with women having higher concentrations than men. The previously noted lower EQU concentrations in NHB compared to NHW were amplified (from 23% to 40%) and NHB were estimated to

have 12–24% lower urine biomarker concentrations compared to NHW for all other phytoestrogens.

In addition to the variables discussed above, we also assessed liver dysfunction for its association with urine phytoestrogen concentrations (data not shown). When added to the model including all sociodemographic variables, lifestyle variables and creatinine, liver dysfunction was not significantly associated with any of the urine phytoestrogens.

Discussion

In this investigation we have studied a selection of frequently used sociodemographic and lifestyle variables, as well as urine creatinine as correlates of 6 urine phytoestrogens in the adult US population. We found that the associations tended to be specific to either a single compound, or a class of compounds originating from a common precursor (e.g. DAZ metabolites, enterolignans), or by a shared mechanism (e.g. mammalian phytoestrogens).

We found that smoking was a significant correlate of DMA and ETL concentrations. Weak but statistically significant negative correlations with serum cotinine were observed for DMA ($r = -0.08$) and ETL ($r = -0.12$), and urine concentrations were estimated to be at least 25% lower in smokers vs. nonsmokers, independent of adjustment for other sociodemographic variables, lifestyle variables or urine creatinine. The association of lower biologic ETL concentrations with smoking has been observed elsewhere. Kilkkinen *et al*. found that serum ETL concentrations in Finnish adults were >26% higher in men and >28% higher in women who were non- or former smokers vs. current smokers, but this association did not remain significant in males after adjustment for other variables ($P = 0.28$) (22). Peeters *et al*. observed in a subset of the EPIC study that smoking explained 2.0% of the total serum ETL variance ($P < 0.05$) and <0.3% of the total serum DMA variance ($P \geq 0.05$) in a model that included age, sex, BMI, and alcohol as well as geographic and laboratory variables (21).

Alcohol consumption was significantly related to DAZ metabolites. Urine EQU and DMA were both negatively correlated with alcohol consumption ($r = -0.11$ in both cases), with urine concentrations estimated to be 18% and 21% lower, respectively with the consumption of 1 alcoholic drink/d vs. none (Model 4). Bolca *et al*. (41) reported that postmenopausal women with higher alcohol intakes were more likely to be strong EQU producers. This appears to contradict our observations with EQU; however, the presence of EQU in the urine is not an absolute indicator of EQU production as dietary exposure is also possible (19). We are not aware of any direct reports of the effect of alcohol consumption on DMA; however, a negative association has been reported for the microbial O-demethylation of isoxanthohumol with alcohol consumption in postmenopausal women (42), and it is plausible that similar phenomena may partially explain the negative association we observed with DMA. Alcohol consumption was not a significant correlate of enterolignan concentrations in our study or elsewhere (22), suggesting that the effects of alcohol on gut metabolism are not straightforward.

We observed that PIR was significantly associated with urine enterolignan concentrations. Both urine ETL and ETD were positively correlated with PIR (r = 0.07 and 0.11, respectively; P <0.05). Urine enterolignan concentrations were 13–18% lower with every 2 unit decrease in PIR across all models. We believe that this relationship is a consequence of dietary patterns associated with PIR. Kerver *et al*. (43) showed in US adults (NHANES III) that PIR was positively correlated with the percentage of individuals in a dietary pattern typified by higher intakes of likely lignan sources (whole grains, fruits and vegetables), and negatively correlated with an antithetic dietary pattern. Kikkinen *et al*. (22) confirmed that positive relationships exist between intake of whole grains, fruits and vegetables and serum ETL levels. In light of this, we believe that the associations observed between urine enterolignans and PIR ostensibly point to a larger pattern of sociodemographic and lifestyle characteristics that influence healthy food choices and, in turn, urine enterolignan concentrations, particularly for ETL. We found that BMI and physical activity were both significant correlates of urine ETL concentrations in patterns consistent with a healthy lifestyle. BMI was negatively correlated such that a 25% increase in BMI was associated with 21% lower ETL levels and physical activity was positively correlated such that an increase in physical activity (MET 750 min/wk vs. 150 min/wk) associated with >6% higher ETL concentrations after covariate adjustment (Model 4).

Interestingly, dietary supplement use was not significantly associated with any of the urine phytoestrogens measured. Although dietary supplement use is quite common in the US population, we suspect that isoflavone and lignan exposure through dietary supplement usage is actually quite low. Bailey *et al*. (44) reported from NHANES 2003–2006 that the prevalence of dietary supplement usage (± SE) in the US population was 39 ± 1% for persons aged 19–30 y and increased to 71 ± 1% for persons ≥71 y. However, if we only consider botanical supplement use–since isoflavones and/or lignans are less likely to be constituents of other supplement types (multi-vitamin/multi-mineral, amino acid)–the prevalence of usage was much lower, ranging from 13 ± 1% (19–30 y) to 20 ± 1% (51–70 y). Additionally, most isoflavone and lignan supplements are marketed based on phytoestrogenic structure-function claims (45) and their use is often targeted to specific populations (e.g., peri- and postmenopausal women) and likely makes up only a fraction of overall botanical dietary supplement use. Finally, in the case of the isoflavone supplements, the amount of isoflavones found in these supplements may be moderate or low when compared to the amounts available in typical servings of soy-based foods (46).

In addition to sociodemographic and lifestyle variables, we included urine creatinine in our analyses due to its established relationship with urine biomarker measurements. In a study of 22 245 participants from NHANES III (1988–1994), Barr *et al*. (47) showed that sex, race-ethnicity and age were significant determinants of creatinine concentration. Creatinine levels tended to be higher in men vs. women and NHB vs. NHW, and decreased with increasing age for adults (≥20 y). We observed that urine creatinine was the most prominent correlate of urine phytoestrogen concentrations out of all variables studied. We found that urine creatinine, when included in the model adjusted for sociodemographic and lifestyle variables, was the strongest correlate of urine concentration for all phytoestrogens.

In this work we have demonstrated to what extent commonly studied sociodemographic and lifestyle variables were correlates of urine phytoestrogen concentrations in the US population (NHANES 2003–2006), and found that these relationships were most often compound- or class-specific. We believe our study has two key strengths that make it a valuable addition to the field of phytoestrogen research. First, it is a unique work in that no other study has examined the relationship of as many sociodemographic and lifestyle variables across as many phytoestrogenic biomarkers in NHANES or in any comparable representative population subset. Second, a standardized analysis approach (40) was used in our study that enables the comparison of our findings to those presented for other nutritional and dietary biomarkers from the same NHANES period (26–29), and presents our data in a format consistent with reference works such as the *Nutrition Report* (14,15). We do acknowledge that there are limitations to our study design and that further study in the context of additional variables is warranted. While we have summarized general patterns of urine phytoestrogen concentrations with respect to a selected set of sociodemographic and lifestyle variables, a limited amount of the total variability was explained ($R^2 \leq 4\%$) suggesting other important variables related to phytoestrogens exist. Therefore, caution should be exercised in interpreting *beta* coefficients from these models as they provide limited model fit and may be biased if an important variable has been omitted. Urine creatinine provides a good example of this; 8–17% of the variability observed was explained when urine creatinine was included in the linear regression models adjusted for sociodemographic and lifestyle variables versus 1–4% when it was not, and the *beta* coefficients for race-ethnicity and BMI showed dramatic changes when urine creatinine was added to the model. Dietary intake is likely the most obvious determinant of biomarker status not included in our analyses. We did not include dietary intake in this study for two reasons. First, isoflavone and lignan intake data is not readily available for the NHANES 2003–2006 and calculating this from the available dietary intake data would be a significant undertaking. Second, our analysis was designed to examine how the concentrations of urine phytoestrogens were associated with selected variables after adjusting for sociodemographic and lifestyle variables, and in that context isoflavone and lignan intakes would serve more so as outcome variables as opposed to covariates. We also did not study pre-analytical and physiological variables (e.g., fasting, time of specimen collection, renal function, inflammation); however, these have been studied separately in an accompanying work (48). Nonetheless, our study of sociodemographic and lifestyle variables as correlates of urine phytoestrogen concentration does serve as a valuable first step in identifying covariates that, together with significant pre-analytical variables, should be considered in future studies examining dietary intake or chronic disease risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Spearman correlation coefficients describing bivariate associations between urine phytoestrogens and selected continuous sociodemographic and lifestyle variables for adults ≥20 y, NHANES 2003–2006[1]

Variable	Genistein	Daidzein	Equol	DMA[2]	Enterodiol	Enterolactone
Age	0.02	0.02	−0.08*	0.02	0.01	0.06*
PIR	−0.01	0.02	0.06*	0.09*	0.11*	0.07*
Smoking (serum cotinine)	−0.03	−0.04	0	−0.08*	−0.03	−0.12*
Alcohol consumption[3]	−0.02	−0.06	−0.11*	−0.11*	0.02	−0.04
BMI	0.01	0.04	0.05*	0.04	0.02	−0.08*
Physical activity[4]	0.03	0.02	0.04	0	0.04	0.09*
Urine creatinine	0.30*	0.30*	0.40*	0.18*	0.32*	0.22*

[1] Excludes individuals who reported antibiotic use in the past 30 d. Sample sizes for urine phytoestrogens by variable are given in Supplemental Table 1.

[2] DMA: O-desmethylangolensin.

[3] Calculated as average daily number of “standard” drinks, i.e. (quantity×frequency)/365.25; 1 drink ≈ 15 g ethanol.

[4] Calculated as total metabolic equivalent task (MET)-min/wk based on self-reported leisure time physical activity.

* Significant correlation. $P < 0.05$.

Table 2

Unadjusted phytoestrogen biomarker concentrations by sociodemographic and lifestyle variables for adults ≥20 y, NHANES 2003–2006[1,2]

Variable	Genistein	Daidzein	Equol	DMA[3]	Enterodiol	Enterolactone
Sociodemographic						
Age, *y*						
20–39	28.9 (25.3–33.0)	62.2 (53.5–72.3)	8.62 (7.55–9.84)	4.25 (3.57–5.07)	39.2 (34.6–44.5)	278 (239–323)
40–59	28.7 (25.4–32.5)	62.9 (56.0–70.6)	6.88 (6.00–7.88)	4.57 (3.92–5.33)	38.8 (32.3–46.6)	285 (244–334)
≥60	29.7 (26.2–33.6)	61.0 (52.7–70.6)	6.97 (6.02–8.07)	4.39 (3.64–5.30)	38.9 (34.4–44.0)	337 (296–385)
P-value[4]	*0.93*	*0.94*	*0.0118*	*0.82*	*0.99*	*0.16*
r^2 (%)[5]	*<1*	*<1*	*<1*	*<1*	*<1*	*<1*
Sex						
Males	31.9 (29.1–35.1)	68.1 (61.1–76.0)	7.88 (7.15–8.68)	4.26 (3.67–4.96)	40.5 (35.4–46.4)	302 (266–343)
Females	26.4 (23.6–29.6)	57.0 (51.2–63.4)	7.19 (6.40–8.07)	4.55 (3.99–5.19)	37.6 (33.5–42.1)	285 (247–329)
P-value[4]	*0.0152*	*0.0147*	*0.15*	*0.49*	*0.38*	*0.56*
r^2 (%)[5]	*<1*	*<1*	*<1*	*<1*	*<1*	*<1*
Race-ethnicity						
Mexican-American	27.9 (25.2–31.0)	52.0 (47.0–57.5)	5.19 (4.64–5.81)	1.98 (1.62–2.41)	38.4 (32.0–46.0)	327 (277–386)
Non-Hispanic black	29.1 (23.7–35.8)	69.0 (56.9–83.8)	6.20 (5.44–7.07)	4.71 (3.67–6.05)	37.7 (33.1–42.9)	285 (246–329)
Non-Hispanic white	28.3 (25.9–31.0)	60.3 (54.5–66.6)	8.12 (7.34–8.99)	4.71 (4.20–5.28)	38.9 (34.7–43.6)	291 (259–327)
P-value[4]	*0.29*	*0.0129*	*<0.0001*	*<0.0001*	*0.16*	*0.69*
r^2 (%)[5]	*<1*	*<1*	*<1*	*1*	*<1*	*<1*
Education						
<High school	32.5 (27.7–38.1)	62.3 (50.9–76.4)	6.66 (5.72–7.74)	3.29 (2.46–4.39)	34.9 (30.1–40.3)	283 (236–340)
High school	26.6 (23.0–30.7)	58.4 (49.9–68.3)	7.15 (6.03–8.47)	4.01 (3.32–4.84)	32.1 (27.3–37.6)	256 (210–312)
>High school	29.1 (26.0–32.5)	63.8 (56.6–72.0)	7.98 (7.13–8.92)	5.04 (4.37–5.81)	43.9 (38.7–49.7)	315 (280–354)
P-value[4]	*0.26*	*0.69*	*0.16*	*0.0302*	*0.0096*	*0.22*
r^2 (%)[5]	*<1*	*<1*	*<1*	*<1*	*<1*	*<1*
PIR[6]						
Low	30.7 (27.8–33.9)	62.3 (55.3–70.2)	6.60 (5.93–7.34)	3.74 (3.00–4.66)	31.9 (27.4–37.1)	258 (218–304)
Medium	28.8 (24.3–34.2)	61.1 (51.6–72.4)	7.70 (6.57–9.03)	4.07 (3.37–4.91)	41.5 (37.1–46.6)	291 (249–341)

Variable	Genistein	Daidzein	Equol	DMA[3]	Enterodiol	Enterolactone
High	28.3 (24.8–32.3)	63.0 (53.8–73.9)	8.18 (7.20–9.31)	5.19 (4.39–6.13)	43.7 (36.5–52.4)	327 (289–369)
P-value[4]	*0.67*	*0.96*	*0.0098*	*0.0465*	*0.0038*	*0.0183*
r^2 (%)[5]	*<1*	*<1*	*<1*	*<1*	*<1*	*<1*
Lifestyle						
Smoking[7]						
No	29.6 (26.9–32.5)	64.5 (58.7–70.9)	7.78 (7.00–8.65)	5.02 (4.43–5.69)	40.6 (36.5–45.2)	337 (308–370)
Yes	27.4 (24.3–30.9)	56.3 (47.3–67.0)	7.03 (6.28–7.87)	3.30 (2.64–4.13)	36.1 (32.0–40.8)	221 (182–268)
P-value[4]	*0.31*	*0.17*	*0.17*	*0.0031*	*0.11*	*0.0002*
r^2 (%)[5]	*<1*	*<1*	*<1*	*<1*	*<1*	*1*
Alcohol consumption[8]						
No drinks	29.6 (26.4–33.2)	67.5 (59.7–76.4)	7.18 (6.36–8.10)	5.15 (4.30–6.15)	34.8 (28.7–42.3)	273 (233–320)
>0–<1 drinks/d	29.1 (25.4–33.3)	61.9 (53.9–71.1)	8.20 (7.38–9.12)	4.67 (4.01–5.44)	40.5 (35.3–46.5)	318 (281–360)
≥1–<2 drinks/d	25.7 (18.2–36.2)	52.5 (36.9–74.7)	6.68 (4.94–9.04)	3.45 (2.24–5.32)	43.5 (31.4–60.3)	284 (193–418)
≥2 drinks/d	25.6 (18.0–36.4)	51.1 (37.0–70.4)	4.75 (3.49–6.45)	2.17 (1.50–3.15)	39.6 (29.9–52.6)	213 (138–329)
P-value[4]	*0.82*	*0.26*	*0.0031*	*<0.0001*	*0.43*	*0.22*
r^2 (%)[5]	*<1*	*<1*	*<1*	*<1*	*<1*	*<1*
BMI[9]						
Underweight	21.6 (11.2–41.7)	28.5 (15.6–52.0)	6.55 (3.01–14.3)	1.59 (.780–3.25)	32.7 (17.5–61.3)	284 (139–581)
Normal weight	29.3 (24.0–35.7)	60.5 (49.2–74.4)	7.33 (6.22–8.64)	4.52 (3.75–5.45)	40.1 (33.6–47.9)	342 (288–407)
Overweight	28.4 (25.1–32.2)	62.3 (55.6–69.6)	7.16 (6.37–8.04)	4.19 (3.51–5.00)	38.2 (33.0–44.2)	298 (261–340)
Obese	29.4 (27.2–31.8)	65.6 (59.4–72.4)	8.07 (7.32–8.90)	4.73 (4.01–5.57)	39.8 (35.0–45.1)	253 (221–290)
P-value[4]	*0.73*	*0.0249*	*0.53*	*0.0021*	*0.86*	*0.0484*
r^2 (%)[5]	*<1*	*<1*	*<1*	*<1*	*<1*	*<1*
Physical activity[10]						
None	29.5 (26.5–32.7)	63.3 (55.4–72.3)	6.59 (5.61–7.75)	3.72 (3.06–4.51)	34.8 (28.9–41.9)	254 (217–298)
>0–<500	25.5 (21.5–30.3)	57.2 (47.6–68.9)	7.39 (6.26–8.72)	4.62 (3.76–5.68)	35.3 (30.3–41.1)	250 (212–295)
≥500–<1000	30.1 (24.0–37.8)	60.6 (48.8–75.4)	8.01 (6.75–9.52)	4.68 (3.50–6.26)	45.9 (36.8–57.2)	349 (278–439)
≥1000	30.6 (25.2–37.2)	64.6 (53.5–78.0)	8.65 (7.57–9.89)	4.82 (3.89–5.98)	43.7 (37.1–51.6)	354 (315–398)
P-value[4]	*0.34*	*0.74*	*0.06*	*0.14*	*0.07*	*0.0006*

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Variable	Genistein	Daidzein	Equol	DMA[3]	Enterodiol	Enterolactone
r^2 (%)[5]	*<1*	*<1*	*<1*	*<1*	*<1*	*<1*
Supplement use[11]						
Yes	28.8 (26.1–31.8)	60.8 (55.4–66.6)	7.84 (6.90–8.92)	4.88 (4.26–5.58)	40.6 (36.3–45.4)	316 (282–353)
No	29.2 (26.3–32.5)	63.7 (55.8–72.8)	7.17 (6.43–8.00)	3.94 (3.26–4.76)	37.3 (32.7–42.5)	271 (235–312)
P-value[4]	*0.84*	*0.53*	*0.27*	*0.09*	*0.28*	*0.07*
r^2 (%)[5]	*<1*	*<1*	*<1*	*<1*	*<1*	*<1*

[1] Excludes individuals who reported antibiotic use in the past 30 d. Sample sizes for urine phytoestrogens by variable are given in Supplemental Table 1.

[2] Biomarker concentrations expressed as geometric means with 95% CI in parentheses. SI (nmol/L) conversion factors are as follows: genistein, × 3.70; daidzein, × 3.93; equol, × 4.13; O-desmethylangolensin, 3.87; enterodiol, × 3.31; enterolactone, ×3.35.

[3] DMA: O-desmethylangolensin.

[4] Based on Wald F test, which tests for significant differences in at least 1 of the means across a given variable.

[5] r^2 from Model 1 (simple linear regression) using categories as shown.

[6] PIR: family poverty income ratio. Low: ≤1.85; Medium: >1.85–≤3.5; High: >3.5.

[7] Based on serum cotinine concentration. Smoker: >10 μg/L. Non-smoker: ≤10 μg/L.

[8] Categories by increasing alcohol consumption calculated as average daily number of “standard” drinks, i.e. (quantity×frequency)/365.25; 1 drink ≈ 15 g ethanol.

[9] BMI: body mass index (kg/m^2). Underweight: <18.5. Normal weight: ≥18.5–<25.0. Overweight: ≥25.0–<30.0. Obese: ≥30.0.

[10] Categories by increasing degree of leisure time physical activity based on metabolic equivalent task (MET)-min/wk.

[11] Based on reported use of any dietary supplement in the past 30 d.

Table 3

Estimated change in phytoestrogen biomarker concentration with change in covariable after adjusting for sociodemographic and lifestyle variables through chunk-wise modeling using data for adults ≥20 y, NHANES 2003–2006[1,2,3]

Variable	Genistein	Daidzein	Equol	DMA	Enterodiol	Enterolactone
Sociodemographic						
Age, every 10 y increase						
Model 1	2.1	1.3	−4.6*	2.5	−0.1	4.4
Model 2	3.0	2.7	−5.9*	2.0	2.2	6.7*
Model 3	3.4	2.9	−5.6*	1.0	3.3	7.8*
Model 4	9.7*	9.1*	−0.2	6.3	9.2*	12.6*
Sex: female vs. male						
Model 1	−17.2*	−16.4*	−8.8	6.7	−7.3	−5.6
Model 2	−20.8*	−20.4*	−8.3	3.6	−7.6	−3.7
Model 3	−18.8*	−19.7*	−14.7	−4.1	−1.7	−11.5
Model 4	15.6	13.6	18.6*	29.3*	37.1*	14.2
Race-ethnicity[4], NHB vs. NHW						
Model 1	3.0	14.5	−23.6*	0.00	−3.1	−2.3
Model 2	3.5	17.2	−24.2*	10.4	4.4	7.9
Model 3	−1.8	7.7	−24.3*	5.0	1.3	5.6
Model 4	−24.1*	−16.4*	−40.3*	−15.6	−20.5*	−12.3
Race-ethnicity[4], MA vs. NHW						
Model 1	−1.3	−13.8*	−36.1*	−58.0*	−1.4	12.2
Model 2	−5.1	−13.0*	−35.8*	−51.1*	15.7	37.7*
Model 3	−2.7	−15.0	−35.8*	−55.3*	14.9	30.1
Model 4	−3.1	−15.3	−36.1*	−55.3*	14.5	29.7
PIR[5], every 2 unit decrease						
Model 1	1.3	−3.5	−10.7*	−20.5*	−17.1*	−13.9*
Model 2	3.2	−1.3	−5.4	−13.3	−13.1*	−13.3*

Variable	Genistein	Daidzein	Equol	DMA	Enterodiol	Enterolactone
Model 3	−0.7	−3.5	−5.5	−14.3	−15.5*	−13.4*
Model 4	−3.7	−6.4	−8.1	−16.4*	−17.9*	−15.3*
Education, ≤HS vs. >HS						
Model 1	−0.8	−6.1	−13.0	−26.7*	−24.3*	−15.3
Model 2	−1.7	−3.8	−4.1	−16.0	−20.5*	−14.3
Model 3	−4.2	−6.2	0.5	−7.0	−14.5	−6.6
Model 4	−6.8	−8.6	−1.9	−9.5	−16.7	−8.4
Lifestyle						
Smoking[6], yes vs. no						
Model 1	−7.3	−12.8	−9.7	−34.3*	−11.0	−34.5*
Model 3	−5.1	−10.0	−8.1	−28.4*	−8.0	−31.6*
Model 4	−7.8	−12.5	−10.4	−30.0*	−10.5	−33.0*
Alcohol, 1 vs. 0 drink/d[7]						
Model 1	−8.1	−12.9*	−17.9*	−29.9*	9.9	−10.0
Model 3	−6.2	−10.3	−20.8*	−24.0*	10.6	−7.0
Model 4	−2.1	−6.4	−17.5*	−21.2*	15.2*	−4.0
BMI[8], 25% increase						
Model 1	0.0	6.8	3.6	5.2	−1.1	−12.7*
Model 3	−0.7	4.9	2.9	2.8	−2.4	−16.4*
Model 4	−8.3	−3.0	−4.5	−4.0	−9.4*	−21.1*
Physical activity[9], 750 vs. 150 MET-min/wk						
Model 1	0.1	−0.1	5.5*	5.6*	4.9	7.3*
Model 3	0.5	−0.8	2.8	−0.1	2.6	5.0*
Model 4	1.3	−0.00	3.6	0.5	3.4	5.6*
Supplement use[10], yes vs. no						
Model 1	−1.5	−4.7	9.3	23.8	8.8	16.7
Model 3	−0.4	−5.7	9.1	9.1	−0.8	−2.5
Model 4	7.9	2.0	17.6	16.6	6.9	3.3

[1] Excludes individuals who reported antibiotic use in the past 30 d. Sample sizes for urine phytoestrogens by variable are given in Supplemental Table 1.

[2] Percent change (%).

[3] Model 1: simple linear regression. Model 2: multiple linear regression adjusting for sociodemographic variables. Model 3: multiple linear regression adjusting for sociodemographic and lifestyle variables. Model 4: multiple linear regression adjusting for sociodemographic and lifestyle variables, and urine creatinine. Change in covariate was carried out while holding any other variables in the model constant.

[4] MA: Mexican Americans. NHB: non-Hispanic blacks. NHW: non-Hispanic whites.

[5] PIR: family poverty income ratio.

[6] Based on serum cotinine concentration. Yes (smoker): >10 μg/L. No (nonsmoker): ≤10 μg/L.

[7] Calculated as average daily number of “standard” drinks, i.e. (quantity×frequency)/365.25; 1 drink ≈ 15 g ethanol.

[8] BMI: body mass index (kg/m^2).

[9] Calculated as total metabolic equivalent task (MET)-min/wk based on self-reported leisure time physical activity.

[10] Based on reported use of any dietary supplement in the past 30 d.

* Change is significantly different from zero. $P < 0.05$.